Received: 5 August 2022 | Accepted: 10 February 2023

DOI: 10.1002/jso.27219

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

A prognostic score from a multicentric retrospective analysis of patients affected by sarcoma with metachronous lung metastases undergoing metastasectomy

Filippo Tommaso Gallina[1] | Enrico Melis[1] | Luca Bertolaccini[2] | Lorenzo Spaggiari[2] | Michele Rocca[3] | Davide Maria Donati[3] | Marco Chiappetta[4] | Stefano Margaritora[4] | Pietro Bertoglio[5] | Piergiorgio Solli[5] | Marco Mammana[6] | Federico Rea[6] | Elisa Concetta Onesti[7] | Virginia Ferraresi[7] | Isabella Sperduti[8] | Gennaro Ciliberto[9] | Francesco Facciolo[1]

[1]Department of Thoracic Surgery, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[2]Department of Thoracic Surgery, IEO, European Institute of Oncology IRCCS, Milan, Italy

[3]Department of Orthopaedic Oncology, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[4]Thoracic Surgery Deparment, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy

[5]Division of Thoracic Surgery, IRCSS Azienda Ospedaliero-Universitaria, Bologna, Italy

[6]Thoracic Surgery and Lung Transplantation Unit, University-Hospital of Padova, Padova, Italy

[7]UOSD Sarcomas and Rare Tumors, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[8]Biostatistics, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[9]Scientific Direction, IRCSS Regina Elena National Cancer Institute, Rome, Italy

Correspondence

Filippo Tommaso Gallina, Thoracic Surgery Unit, IRCCS Regina Elena National Cancer Institute Via Elio Chianesi 53, 00144 Rome, Italy.
Email: filippogallina92@gmail.com

Abstract

Background: Despite the lack of evidence-based on prospective randomized studies, surgery has become the cornerstone of the treatment in patients with pulmonary oligometastatic sarcomas. Our study aimed to construct a composite prognostic score for metachronous oligometastatic sarcoma patients.

Methods: A retrospective analysis was performed on data patients who underwent radical surgery for metachronous metastases in six research institutes from January 2010 to December 2018. The log-hazard ratio (HR) obtained from the Cox model was used to derive weighting factors for a continuous prognostic index designed to identify differential outcome risks.

Results: A total of 251 patients were enrolled in the study. In the multivariate analysis, a longer disease-free interval (DFI) and a lower neutrophil-to-lymphocytes ratio (NLR) were predictive of a better overall survival (OS) and disease-free survival (DFS). A prognostic score was developed based on DFI and NLR data, identifying 2 risk class groups for DFS (3-years DFS 20.2% for the high-risk group [HRG]and 46.4% for the low-risk group [LRG] [<0.0001]) and 3 risk groups for OS (3 years OS 53.9% for the HRG vs. 76.9% for the intermediate-risk group and 100% of the LRG ($p < 0.0001$)).

Conclusion: The proposed prognostic score effectively predicts outcomes for patients with lung metachronous oligo-metastases from the surgically treated sarcoma.

KEYWORDS

lung cancer, lung metastases, metastasectomy, NLR, sarcoma

1 | INTRODUCTION

Sarcomas are a heterogeneous group of cancers, typically divided into two major groups: bone sarcomas and soft tissue sarcomas, each of which has several subtypes.[1] Metastatic relapse after primary sarcoma treatment is observed with a prevalence for lung location.[2] Based on previous analyses, approximately 20%–25% and up to 40% of all soft tissue and bone sarcoma patients will develop pulmonary metastases, which will usually become clinically evident in the first 2 years following diagnosis.[3] The location, the number, and the time to development of metastases are considered prognostic factors that drive the treatment decisions.[4] In the case of the appearance of lung nodules, the differential diagnosis with other benign or malignant aetiologies (e.g., primary lung cancer) is critical, particularly in a more prolonged disease-free survival (DFS) interval. Despite the lack of data from randomized controlled trials, surgery has become the mainstay of treatment in patients with pulmonary metastatic sarcomas over the last few decades. Five-year survival rates ranging from 15% to >50% following pulmonary metastasectomy in patients with resectable disease have been reported.[5]

In the last few decades, immune system activity has been increasingly accepted as a hallmark of cancer.[6] Lymphocytes, as critical components of the host's anticancer immunity, play essential functions in immunosurveillance and immunoediting and contribute to the inhibition of tumor cell proliferation and migration. Increased circulating blood lymphocytes are a favorable prognostic factor in several cancer types.[7] Neutrophils are recognized as essential components of tumor inflammation.[8] Circulating neutrophils can produce a variety of molecules, including tumor necrosis factor-α, vascular endothelial growth factor, and interleukin, which can promote tumor progression.[9] Recently, emerging evidence supports an important role of systemic inflammation in the prognosis of patients with various sarcomas. Peripheral blood neutrophil-to-lymphocytes ratio (NLR) could predict prognosis in localized soft tissue sarcoma, and it can be used to assess the risk of relapse.[10] Same results were also found for bone sarcoma. Indeed, various inflammatory scores can be used to predict the outcomes of patients with osteosarcoma.[11]

Although multiple risk factors associated with poor survival have been reported, stratification of these variables into patient cohorts to guide surgical treatment is not well defined. Our study performed a multicentric retrospective analysis to determine a prognostic score including clinical and pathological characteristics in patients with oligometastatic sarcomas confined to the lungs.

The objectives of this study were:

To individuate prognostic factors for overall survival (OS) and DFS in patients who underwent pulmonary metastasectomy for sarcoma.

To understand the relationship between systemic inflammation and prognosis of oligometastatic sarcoma using the preoperative NLR.

2 | MATERIAL AND METHODS

The ethics committee of the IRCCS Regina Elena National Cancer Institute approved the study (approval number 1339/20). This is a multicentric retrospective study performed in six high volume thoracic surgery departments with proven experience with pulmonary oligometastatic disease (IRCCS Regina Elena National Cancer Institute from Rome, European Institute of Oncology from Milan, University of Padova, Fondazione Policlinico Universitario A. Gemelli from Rome, IRCCS Istituto Ortopedico Rizzoli from Bologna and IRCCS Azienda Ospedaliera Universitaria from Bologna).

This manuscript was written according to the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) Statement.[12] The STROCSS checklist is available as Supporting Information: File 1.

Sarcoma patients who underwent pulmonary metastases resection at the participating centers from January 2010 to December 2018 were included.

The inclusion criteria were:

- Histologically confirmed diagnosis of soft tissue or bone sarcoma radically resected.
- Metachronous metastases.
- Number of lung metastases ≤ 5.
- Metastasectomy with radical intent.
- Patients with R0 resection.
- No evidence of extra-thoracic metastases.
- Availability of data on preoperative blood venous analysis.
- Patients able to tolerate lung resection.

The exclusion criteria were:

- Patient with other cancers.
- Synchronous metastases.
- Patients with acute and chronic infections at the moment of the venous blood sampling.
- Patients immunosuppressed and under steroid treatments
- Presence of extra-thoracic metastases.
- Number of lung metastases > 5.
- Incomplete metastasectomy (R1−2 resection).
- Patients with incomplete data or without updated follow-up.

Although an inter-center variability in preoperative workup was present, all patients underwent computed tomography (CT) of the brain, the thorax, and the abdomen. At the same time, 18-FDG positron emission tomography (18-FDG PET) was performed in every case of suspected localization when indicated and available. Treatment indication was discussed in multidisciplinary tumor boards, including oncologists, radiotherapists, and thoracic surgeons.

The data collected into the database were: date of birth, gender, years at the diagnosis of lung metastases, smoking history, comorbidities, primary histology, primary tumor site, primary surgery date, postoperative treatments, interoperative interval, histological grade of the primary tumor, onset pulmonary metastases, distribution of pulmonary metastases, number of pulmonary metastases, size of largest lung lesion, PET uptake, type of pulmonary resection, postoperative complications, neutrophils to lymphocytes ratio, postoperative treatment, type of postoperative treatment, recurrences, time to recurrence, last follow-up, vital status, OS and, DFS.

Blood sample analyses performed during the 1 month before surgery were collected to calculate the preoperative NLR, defined as

the ratio of the absolute neutrophil and lymphocyte counts. The postoperative follow up imaging for high-grade sarcoma consisted of magnetic resonance imaging of the primary tumor's region and a chest/abdomen CT every 3 months during the first 2 years. Imaging intervals were prolonged to every 4–6 months during the third year and every 6 months for 5 years. Above 5 years, yearly imaging was discussed on a case-by-case basis.[13,14] All cases were discussed in the multidisciplinary sarcoma meeting, including radiologists, medical and radiation oncologists, and orthopedic and thoracic surgeons.

2.1 | Time-to-event end point definitions

OS was defined as the time between the surgery of the metastasis and the last follow-up or death from all causes.

DFS was defined as the time between the treatment of lung metastasis and the recurrence of sarcoma.

Disease-free interval (DFI) was defined as the interval between the end of the treatment of the primary tumor and the diagnosis of the lung metastasis based on radiologic imaging.

2.2 | Statistical analysis

The statistical methods of risk class generation was summarized on Supporting Information Material 1. Descriptive statistics were used to summarize pertinent study information. Continuous variables were reported as median with the 25th–75th percentile interval. Nominal variables were expressed binarily as the presence or absence of the event and reported as counts and percentages. The Kaplan–Meier method was used to calculate survival rates and draw survival curves. The log-rank test assessed survival differences between the different risk class groups. Significance was defined at the p less than 0.05 level.

The Hazard ratio (HR) and the 95% confidence intervals (95% confidence interval [CI]) were estimated for each variable. Variables testing significantly at univariate analysis were entered into multivariate analysis. A multivariate proportional hazard model with stepwise regression was used (forward selection, enter limit and remove the limit, $p = 0.10$ and $p = 0.15$, respectively) to identify independent predictors of outcomes. The assessment of interactions between significant investigational variables was considered when developing the multivariate model.

The maximally selected log-rank statistics analysis was applied to the continuous variable to estimate the most appropriate cut-off values able to split the patients into groups with different outcome probabilities. Cut-offs allowed transforming continuous into categorical variables, with the aim of finally generating the risk classes.

The SPSS (version 21.0; SPSS, Inc.) licensed statistical program was used for all analyses.

2.3 | Risk class generation

The log-HR obtained from the Cox model was used to derive weighting factors of a categorical prognostic index designed to identify differential risk outcomes.[13] Coefficient estimates were "normalized" by dividing by the smallest one and then rounding the resulting ratios to the nearest value. To address the multivariate model in terms of goodness of fit and to validate the results, a cross-validation technique that evaluated the replication stability of the final Cox multivariate model in predicting all outcomes was also investigated, using a resampling procedure.[14,15] This technique generates 100 simulation data sets (each 80% of the original size) by randomly selecting patients from the original sample to establish the consistency of the model across less-powered patient samples.[16]

3 | RESULTS

According to the inclusion and exclusion criteria, 251 patients were included in the study. The clinical and pathological characteristics are reported in Table 1. All patients showed a high-grade disease. Histopathological analysis showed a bone sarcoma diagnosis in 54 (21.5%) patients and 197 (78.5%) patients with a soft tissue sarcoma diagnosis. The most common histology was leiomyosarcoma (27%), followed by undifferentiated pleomorphic sarcoma (18.7%) and osteosarcoma (10.3%). 117 (46.4%) patients presented at least one comorbidity, the most frequent was hypertension (15.3%). A history of smoking was reported in 94 patients (37.3%). The median age at the diagnosis of the metastasis was 53 years (range 13–82). Anatomical pulmonary resection (segmentectomies or lobectomies) was performed in 38 (15.1%) patients, while the remainder underwent wedge resection. 23 (9.2%) patients underwent bilateral pulmonary resection. After the metastasectomy, 73 (29.0%) patients underwent chemotherapy. The median preoperative NLR count was 3.00 (range 0.34–19.89). The median time (months) between the primary tumor resection and the metastasis resection was 20.50 (range 3–199). The median follow-up was 28.27 (range 3–154) months. During the follow-up, 161 (64.1%) patients showed a recurrence and 109 (43.4%) patients died.

The univariate analysis was performed using the following features: gender, age, smoking status, comorbidities, DFI, type of pulmonary resection, postoperative complications, histology, neo/adjuvant treatments (primary tumor), neo/adjuvant treatments (lung metastasis), size of the largest lesion, number of metastases, and the neutrophils to lymphocytes ratio.

The variables that resulted statistically significant in DFS and OS were the NLR and the DFI (Supp.). The multivariate analysis showed a statistically significant difference in terms of DFS and OS analyzing the NLR (HR of 1.054 (CI 95% 1.008–1.102, $p = 0.02$) for DFS and HR of 1.079 (CI 95% 1.013–1.149, $p = 0.018$) for OS) and the DFI value (HR of 0.996 (CI 95% 0.993–1.000, $p = 0.025$) for DFS and HR of 0.995 (CI 95% 0.990–1.000, $p = 0.043$) for OS) (Table 2).

TABLE 1 Clinical and pathological features of the population.

Variables	
Gender	
Male (%)	134 (53.4)
Female (%)	117 (46.6)
Age (years)	
Median (25th–75th percentile interval)	53.50 (42–64)
Smoking history	
Yes (%)	94 (37.4)
No (%)	149 (59.4)
Unknown (%)	8 (3.2)
Comorbidities	
Yes (%)	117 (46.6)
No (%)	134 (53.4)
Primary postoperative treatment	
Yes (%)	149 (59.4)
No (%)	102 (40.6)
Type of pulmonary resection	
Anatomic resection (%)	38 (15.1)
Wedge resection (%)	213 (84.9)
Postoperative complications	
Yes (%)	220 (87.3)
No (%)	29 (11.5)
Unknown (%)	2 (0.8)
Secondary postoperative treatment	
Yes (%)	73 (29.0)
No (%)	139 (55.2)
Unknown (%)	39 (15.5)
Histology	
Bone derived sarcoma (%)	54 (21.5)
Soft tissue sarcoma (%)	197 (78.5)
Size of the largest lesion (cm)	
Median (25th–75th percentile interval)	3.5 (1–2.5)
Number of metastases	
Median (25th–75th percentile interval)	2.00 (1.00–2.00)
Neutrophils count (10^9/l)	
Median (25th–75th percentile interval)	4.25 (3.08–6.07)
Lymphocytes count (10^9/l)	
Median (25th–75th percentile interval)	1.40 (1.05–1.09)
Neutrophils-to-Lymphocytes ratio (NLR)	
Median (25th–75th percentile interval)	3.0 (1.88–5.15)

After the codification of the categorical variables, the results were confirmed. Indeed, in the DFS analysis, the DFI showed an HR of 2.438 (CI 95% 1.451–4.097, $p = 0.001$) and the NLR an HR of 2.07 (CI 95% 1.434–3.007, $p = 0.0001$), while for the OS analysis, the DFI showed an HR of 3.439 (CI 95% 1.501–7.881, $p = 0.004$) and the NLR an HR of 3.016 (CI 95% 1.729–5.262, $p = 0.0001$). Using the independent risk factors of the multivariable analysis, a composite prognostic score was built, identifying different patient groups (Table 3).

The DFS analysis showed a low-risk group (LRG, 42.2%) with 0–1 risk factor (score < 2.2) and a high-risk group (HRG, 57.8%) with both risk factors (score ≥ 2.2).

Instead, the OS analysis allows us to identify three different categories:

LRG (3.6%): without risk factors (DFI > 80 months and NLR < 2, score 0).

Intermediate risk group (39.1%): with one risk factor (DFI < 80 months or NLR > 2, score > 0 and <2.1).

HRG (57.3%): with two risk factors (DFI < 80 months and NLR > 2, score ≥ 2.1).

These different groups discriminated against the prognosis of patients who had undergone metastasectomy for sarcoma. The 3-years DFS of the HRG was 20.2%, while in the LRG was 46.4% ($p < 0.0001$) (Figure 1). Furthermore, HRG's 3- and 5-years OS was 53.9% and 33.2% versus 76.9% and 68.2% of the middle-risk versus 100% and 100% of the low-risk ($p < 0.0001$) (Figure 2). The robustness of the multivariate model was investigated by the cross-validation technique with a replication rate ranging from 92% to 96% for 100 simulated data set.

4 | DISCUSSION

In this study, we evaluated the outcomes and the prognostic factors of the patients with metachronous oligometastatic sarcoma after the radical pulmonary resections. Much attention was focused on the systemic inflammation score represented by the NLR, finding that this parameter predicts survival outcomes in a significant way. Moreover, we identified a significant cut-off of 2 that permitted categorizing patients and defining prognosis associated with the DFI.

Studying serum biomarkers involved in the inflammatory response to cancer is an area of research that has gained increased attention in recent years.[17] Furthermore, deranged systemic inflammation expressed by NLR elevation may induce the so-called CD4+ lymphocyte Th1/Th2 shift, with an inhibition of the former. CD4+ Th1 lymphocytes play essential functions in immunosurveillance and immunoediting and contribute to the inhibition of tumor cell proliferation and migration. They also exert a pernicious effect on target cells and induce tumor cell apoptosis.[18]

Circulating inflammatory cells can affect the tumor microenvironment and may change the aggressiveness of the disease.

TABLE 2 Multivariate analysis with categorized variables for OS and DFS.

Variables	Multivariable DFS			Multivariable OS		
	HR (95% CI)	*p* Value	Replication rate (internal validation)	HR (95% CI)	*p* Value	Replication rate (internal validation)
Disease-free interval ≤ 80 versus >80	2.438 (1.451–4.097)	0.001	96%	3.439 (1.501–7.881)	0.0001	96%
Neutrophils to Lymphocytes ratio ≤ 2.0 versus >2.0	2.077 (1.434–3.007)	0.0001	92%	3.016 (1.729–5.262)	0.004	92%

TABLE 3 Risk factors determine prognostic score and risk group classification (Supporting Information: Material 1).

	Score
Disease-free Survival (DFS)	
NLR > 2	1
Disease-free Interval < 80	1.2
Low risk if score < 2.2	
High risk if score ≥ 2.2	
Overall survival (OS)	
NLR > 2	1
Disease-free Interval < 80	1.1
Low risk if score 0	
Intermediate risk if score > 0 < 2.1	
High risk if score ≥ 2.1	

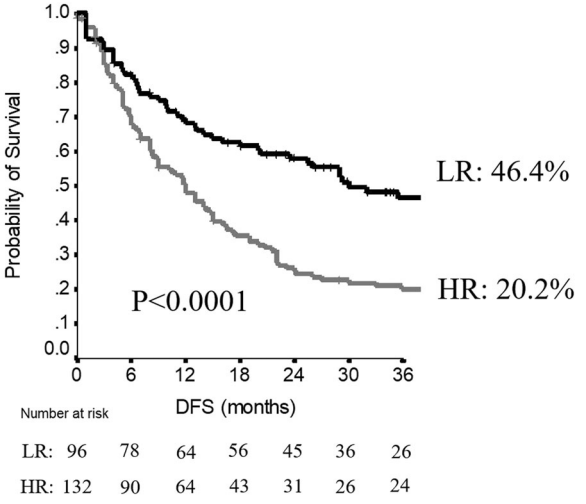

FIGURE 1 Three years disease-free survival (DFS) in patients of high-risk group (HR) and low-risk group (LR).

Some studies showed that neutrophils have a fundamental role in inflammatory responses, but their contribution to tumorigenesis remains controversial. In a preclinical model of breast cancer, using various strategies to block neutrophil recruitment to the pre-metastatic site demonstrated that neutrophils specifically support metastatic initiation. Indeed, neutrophil-derived leukotrienes can aid the colonization of distant tissue by selectively expanding the sub-pool of cancer cells that retain high tumorigenic potential.[19]

The importance of lymphocytes has been highlighted in several studies in which increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients.[20]

Only a few studies have been published investigating inflammatory serum biomarkers in sarcoma tumors. In 2013 and 2015, Szkandera et al. reported an association between NLR and DFS and

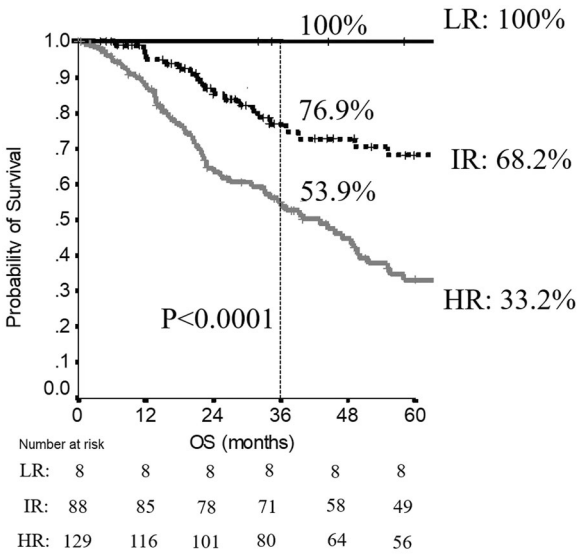

FIGURE 2 Three years and five years Overall Survival (OS) in patients of high-risk group (HR), intermediate-risk group (IR) and low-risk group (LR).

OS in sarcoma patients. They reported a DFS of 77.9 versus 99.1 months in a 260 sarcoma patients cohort and found a cut-off value of 3.45. Later they found NLR > 2.39 associated with worse DSF and OS in a larger cohort.[21]

Aggerholm-Pedersen et al. studied the prognostic value of serum biomarkers (albumin, C-reactive protein, serum sodium, hemoglobin, neutrophils, and lymphocytes) in combination in patients with metastatic sarcoma. They showed that in a cohort of 281 patients with metastatic sarcoma, all six investigated serum biomarkers were independent prognostic factors for DFS.[22]

In the last few years, C-reactive protein was also analyzed to predict prognosis in patients with several cancers. Wang et al. in a recent meta-analysis, showed that elevated pretreatment serum CRP level could serve as an independent risk factor for poor prognosis in patients with soft tissue sarcoma.[23]

These studies refer to the sarcoma tumors at different stages and the inflammatory index associated with the prognosis in all the cases. In our study that analyzed a specific cohort of patients with the metachronous oligometastatic condition, the results agree with the literature showing a prognostic relevance of NLR.

Another decisive prognostic factor resulted in the DFI, with a significant survival improvement over 80 months. Many studies in the literature showed how the DFI is associated with the prognosis of the patients. Pastorino et al. analyzing the "international registry of lung metastases," identified how a DFI under 36 months is associated with the worst prognosis.[24] Generally, in some subsequent studies, the cut-off of DFI changes between 12 and 35 months. In a retrospective analysis of 120 patients with metastatic sarcoma, Dossett et al. identified that patients with a DFI lesser than 13 months had the worst prognosis.[25] Van Geel et al. in a soft tissue metastatic sarcoma patients analysis have found a cut-off for DFI of 31 months to define the prognosis.[26] The inclusion criteria of these studies did not limit the number of metastases resected, and the synchronous metastases were also included. The significant variability of these cut-offs was probably referred to the relevant differences in the selection criteria of these studies.

In our analysis, the DFI resulted statistically significant in terms of DFS and OS as a continuous variable and after the cut-off codification. Therefore, our study has shown a DFI cut-off of 80 months to predict the prognosis. This value is greater than the other studies in the literature, probably due to the strict selection of our cohort. Thus, we selected only oligometastatic (less than 5 pulmonary metastases) patients with metachronous lesions. To our knowledge, this is one of the first studies using these inclusion criteria.

Our univariate analysis showed that the prognosis is not affected by the number of metastases and the tumor histology (bone/soft tissue). Usually, the number of resected metastases, the size, and the bilateral or unilateral nature of the disease represent a significant prognostic factor.[27] However, other studies did not demonstrate a difference in outcomes between patients with metastatic soft tissue sarcoma or bone-derived sarcoma with more than 4 lesions. Nevertheless, the best outcomes are uniformly carried out when complete resection is achieved.[28]

According to the guidelines, surgery is considered the first option to treat lung metastases from sarcoma. Indeed, the use of alternative treatments such as the stereotactic body radiation therapy are reserved for patients unsuitable for surgery.[29] In our analysis, the type of resection did not show any differences between the anatomic and the wedge resection in terms of prognosis. Some studies in the literature showed that if safe resection margins are possible, anatomic lung resection, such as segmentectomy or lobectomy, does not improve the outcomes compared to wedge resection.[30] However, anatomic resection is needed for the central lesions that are technically challenging to remove. In these cases, segmentectomy should be the first option to achieve a complete resection because it allows us to spare the lung parenchyma and limit the loss of pulmonary function.[30] Given that metastatic sarcoma frequently shows multiple lung recurrences, the lung parenchyma sparing surgery should be considered pivotal. Consequently, the most common intervention performed in case of metastasis is the wedge resection, especially for a few nodules that minimally invasive approaches can safely approach.[31]

To decrease the risk of local or distant recurrence, in specific subset of sarcomas before or after the radical surgical resection a chemotherapy and or radiotherapy can be administered. According to the guidelines the management of resectable soft tissue sarcoma is mainly focused on the surgery and in case of R1 resection or in high risk R0 resection could be added an adjuvant radiotherapy. However, in case of a bone sarcoma, the treatment could be focused on the surgery alone for the low risk osteosarcoma while in case of high risk osteosarcoma and Ewing sarcoma surgery is combined to a neoadjuvant and adjuvant chemotherapy.[32,33] Therefore, we evaluated the prognostic role of chemotherapy or radiotherapy in neo/adjuvant setting during the treatment of the primary tumor. As reported in the Supporting Information Materials, our univariate analysis did not show any significant differences. Despite the retrospective nature of the study and the risks of bias, we can

assume that in a context of a homogeneous cohort of patients with an oligometastatic disease these parameters did not influence the prognosis.

Postoperative chemotherapy after metastasectomy did not represent a prognostic factor in our cohort. As reported in the literature, the use of chemotherapy in a patient with metastatic sarcoma is still debated. Indeed, in a recent retrospective analysis of 580 patients with soft tissue sarcomas and lung metastases treated in EORTC trials and receiving first-line chemotherapy, as anthracycline-containing combinations, the 3-years OS proved to be less than 20% also for lung metastases only so, confirming the palliative role of systemic treatment.[34]

Our study showed how also, in a cohort of patients strictly selected, all eligible for radical surgery, long term outcomes are influenced by two significant variables such as NLR and DFI. We constructed a composite prognostic score that can predict the prognosis using these two accessible parameters. The best results in terms of OS and DFS have been obtained in patients with prolonged DFI and lower NLR. The OS analysis showed an intermediate group that presented only one risk factor, DFI less than 80 months or NLR > 2.

Using these two simple variables in clinical practice may help better stratify the patient with sarcoma metastases. It could lead to a better selection of patients potentially eligible for surgery. This prognostic score can be cost-effectively applied to new cases to predict prognosis in oligometastatic lung patients affected by soft tissue or bone sarcoma.

This study also has some limitations. First, the project was a retrospective, non-randomized study leading to selection bias. The presence of comorbidities may represent a selection bias due to the influence of inflammation-associated diseases. However, we only selected patients without acute inflammatory disease at the moment of the blood sample withdrawal. The patients' selection was extended from 2010 until 2018. During this period, the diagnostic and therapeutic algorithms changed substantially, especially in terms of chemo or radiotherapy regimens after the primary tumor or the metastases resection. Indeed, notwithstanding the use of rigid inclusion criteria, the extended follow up period entails the heterogeneous nature of the oncological treatment of the patients.

Nevertheless, only universities or research institutions with consolidated experience in sarcoma management were involved. Another limitation was the absence of an external data set for independent validation. However, we conducted a cross-validation technique to assess our model's stability and replicability to confirm our score's validity, following the literature data.

In conclusion, our study showed that in a selected cohort of metachronous oligometastatic patients, NLR and DFI are two variables that can predict the prognosis easily with no additional costs as these data are already available for all patients and can be easily applied in clinical practice. NLR and DFI were used to construct a prognostic score that classified patients into two groups for DFS and three risk groups for OS.

ACKNOWLEDGMENTS

The authors want to thank the Scientific Direction of the IRCCS "Regina Elena" National Cancer Institute for supporting our work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, FTG, upon reasonable request.

ORCID

Filippo Tommaso Gallina http://orcid.org/0000-0001-5579-0837
Luca Bertolaccini http://orcid.org/0000-0002-1153-3334
Marco Chiappetta http://orcid.org/0000-0002-3807-6911
Pietro Bertoglio http://orcid.org/0000-0002-6267-0099

REFERENCES

1. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49(3):684-695.
2. Kon Z, Martin L. Resection for thoracic metastases from sarcoma. *Oncology (Williston Park, N.Y.)*. 2011;25(12):1198-1204.
3. Kang S, Kim H-S, Kim S, Kim W, Han I. Post-metastasis survival in extremity soft tissue sarcoma: a recursive partitioning analysis of prognostic factors. *Eur J Cancer*. 2014;50(9):1649-1656.
4. Marulli G, Mammana M, Comacchio G, Rea F. Survival and prognostic factors following pulmonary metastasectomy for sarcoma. *J Thorac Dis*. 2017;9(suppl 12):S1305-S1315.
5. Okiror L, Peleki A, Moffat D, et al. Survival following pulmonary metastasectomy for sarcoma. *Thorac Cardiovasc Surg*. 2016;64(2):146-149.
6. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444.
7. Iseki Y, Shibutani M, Maeda K, et al. The impact of the preoperative peripheral lymphocyte count and lymphocyte percentage in patients with colorectal cancer. *Surg Today*. 2017;47(6):743-754.
8. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *JNCI*. 2014;106(6):dju124.
9. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer*. 2017;16(1):137.
10. Jiang L, Jiang S, Situ D, et al. Prognostic value of monocyte and neutrophils to lymphocytes ratio in patients with metastatic soft tissue sarcoma. *Oncotarget*. 2015;6(11):9542-9550.
11. Yang Q, Chen T, Yao Z, Zhang X. Prognostic value of pre-treatment naples prognostic score (NPS) in patients with osteosarcoma. *World J Surg Oncol*. 2020;18(1):24.
12. Mathew G, Agha R, Albrecht J, et al. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. *Int J Surg*. 2021;96:106165.
13. Di Maio M, Lama N, Morabito A, et al. Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. *Eur J Cancer*. 2010;46(4):735-743.
14. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med*. 1992;11(16):2093-2109.

15. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364-1370. doi:10.1200/JCO.2007.12.9791
16. Bria E, Milella M, Sperduti I, et al. A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer. *Lung Cancer*. 2009;66(3):365-371.
17. Kitamura T, Qian B-Z, Pollard JW. Immune cell promotion of metastasis. *Nat Rev Immunol*. 2015;15(2):73-86.
18. Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. *J Immunol*. 1985;134(1):230-234.
19. Wculek SK, Malanchi I. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. *Nature*. 2015;528(7582):413-417.
20. Malkova AM, Sharoyko VV, Zhukova NV, Gubal AR, Orlova RV. Laboratory biomarkers of an effective antitumor immune response. Clinical significance. *Cancer Treat Res Commun*. 2021;29:100489.
21. Szkandera J, Gerger A, Liegl-Atzwanger B, et al. The derived neutrophil/lymphocyte ratio predicts poor clinical outcome in soft tissue sarcoma patients. *Am J Surg*. 2015;210(1):111-116.
22. Aggerholm-Pedersen N, Maretty-Kongstad K, Keller J, Safwat A. Serum biomarkers as prognostic factors for metastatic sarcoma. *Clin Oncol*. 2019;31(4):242-249.
23. Wang X, Liu S, Zhao X, Fang E, Zhao X. The value of C-reactive protein as an independent prognostic indicator for disease-specific survival in patients with soft tissue sarcoma: a meta-analysis. *PLoS One*. 2019;14(7):e0219215.
24. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997;113(1):37-49.
25. Dossett LA, Toloza EM, Fontaine J, et al. Outcomes and clinical predictors of improved survival in a patients undergoing pulmonary metastasectomy for sarcoma. *J Surg Oncol*. 2015;112(1):103-106.
26. van Geel AN, Pastorino U, Jauch KW, et al. Surgical treatment of lung metastases: the european organization for research and treatment of cancer-soft tissue and bone sarcoma group study of 255 patients. *Cancer*. 1996;77(4):675-682.
27. Welter S, Grabellus F, Bauer S, et al. Growth patterns of lung metastases from sarcoma: prognostic and surgical implications from histology. *Inter Cardiovasc Thorac Surg*. 2012;15(4):612-617.
28. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". *J Thorac Oncol*. 2011;6(8):1373-1378.
29. Navarria P, Baldaccini D, Clerici E, et al. Stereotactic body radiation therapy for lung metastases from sarcoma in oligometastatic patients: a phase 2 study. *Int J Radiat Oncol Biol Phys*. 2022;114(4):762-770.
30. Berry MF. Role of segmentectomy for pulmonary metastases. *Ann Cardiothorac Surg*. 2014;3(2):176-182.
31. Perentes JY, Krueger T, Lovis A, Ris H-B, Gonzalez M. Thoracoscopic resection of pulmonary metastasis: current practice and results. *Crit Rev Oncol Hematol*. 2015;95(1):105-113.
32. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv51-iv67.
33. Casali PG, Bielack S, Abecassis N, et al. Bone sarcomas: ESMO-PaedCan-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv79-iv95.
34. Lindner LH, Litière S, Sleijfer S, et al. Prognostic factors for soft tissue sarcoma patients with lung metastases only who are receiving first-line chemotherapy: an exploratory, retrospective analysis of the european organization for research and treatment of cancer-soft tissue and bone sarcoma. *Int J Cancer*. 2018;142(12):2610-2620.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gallina FT, Melis E, Bertolaccini L, et al. A prognostic score from a multicentric retrospective analysis of patients affected by sarcoma with metachronous lung metastases undergoing metastasectomy. *J Surg Oncol*. 2023;127:1035-1042. doi:10.1002/jso.27219